The Journal of Clinical Endocrinology & Metabolism, 2023, **108**, e1074–e1081
https://doi.org/10.1210/clinem/dgad214
Advance access publication 18 April 2023
Clinical Research Article

Serum scEMC10 Levels are Negatively Associated With Resting Metabolic Rate and age in Humans

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Abstract

Context: We have recently shown that the secreted isoform of endoplasmic reticulum membrane complex subunit 10 (scEMC10) is upregulated in human obesity and that overexpression of scEMC10 promotes, whereas antibody neutralization of circulating scEMC10 prevents diet-induced obesity in mice.

Objective: To explore associations of serum scEMC10 with body mass index (BMI), resting metabolism rate (RMR), and age in humans.

Design: A cross-sectional study.

Setting and Patients: A total of 833 participants from a Chinese physical examination cohort and 191 participants from the Leipzig Obesity Biobank cohort.

Main Outcome Measures: Serum scEMC10 concentrations are measured using chemiluminescent immunoassay. RMR is calculated based on measurements from indirect calorimetry with an open-circuit ventilated-hood system.

Results: In the Chinese physical examination cohort, a J-shaped nonlinear correlation between BMI and serum scEMC10 was identified in participants where underweight, overweight, and obese people all presented higher serum scEMC10 levels than normal weight people. Participants younger than age 30 years old exhibited significantly higher serum scEMC10 levels than those older than 50 years of age. In addition, participants aged 30 to 40 years also had significantly higher serum scEMC10 levels than those aged 50 to 60 years. In the Leipzig Obesity Biobank cohort, we observed a significantly negative correlation between serum scEMC10 and resting energy expenditure after adjusting for BMI. Participants in the highest quartile of serum scEMC10 levels had significantly lower RMR than those in the first quartile. RMR had an independently inverse association with serum scEMC10.

Conclusions: Serum scEMC10 levels are negatively associated with age and RMR in humans.

Key Words: scEMC10, BMI, age, resting metabolism rate

Abbreviations: ALT, alanine aminotransferase; AST, aminotransferase; BAT, brown adipose tissue; BMI, body mass index; BSA, body surface area; EMC10, endoplasmic reticulum membrane complex subunit 10; FPG, fasting blood glucose; scEMC10, secreted endoplasmic reticulum membrane complex subunit 10; GGT, gamma-glutamyl transferase; LDL-C, low-density lipoprotein cholesterol; REE, resting energy expenditure; RMR, resting metabolism rate; TG, triglyceride.

Endoplasmic reticulum membrane complex subunit 10 (EMC10) is evolutionarily conserved across species. Both human and mouse EMC10 exist as 2 isoforms: secreted EMC10 (scEMC10) and membrane-bound EMC10 (1). scEMC10, also known as INM02 and hHSS1, was cloned by our group in insulinoma tissue for the first time and found to be upregulated by high glucose in pancreatic β cells (2-4). We have recently presented evidence that overexpression of scEMC10 promotes, whereas specific antibody neutralization of circulating scEMC10 prevents, diet-induced obesity and related metabolic diseases in mice (5). These phenotypes are attributed to inhibitory effects of scEMC10 on adipocyte thermogenesis (5). Although we observed that circulating scEMC10 is increased in obesity and is positively associated with body mass index (BMI) in humans (5), the effect of scEMC10 on human energy expenditure has not been characterized.

Resting energy expenditure (REE) accounts for 60% to 70% of total energy expenditure and is defined as the minimum

Received: 18 January 2023. **Editorial Decision:** 10 April 2023. **Corrected and Typeset:** 17 May 2023

energy required for the body to perform vital functions under basal conditions (6). Given that obesity is a disorder of energy balance, we sought to examine the relationship between circulating scEMC10, a pro-obesity hormone, and resting metabolic rate (RMR), the adjusted REE, in humans. Because age is 1 of the most important contributors to energy metabolism (7), the correlation between serum scEMC10 and age will also be investigated.

Here, we show circulating scEMC10 is inversely correlated with RMR in participants from the Leipzig Obesity Biobank cohort and is negatively associated with age in participants from a Chinese physical examination cohort and. In addition, serum scEMC10 is positively associated with BMI in participants of the 2 cohorts.

Patients and Methods

Patients

We recruited 883 participants who underwent physical examinations and routine blood biochemical analyses at Huashan Hospital from September to October 2017. Participants with the following conditions were excluded in this study: (1) hemoglobin <90 g/L; (2) white blood cell count >10× 10^9/L; (3) alanine aminotransferase (ALT) >150 U/L; and (4) Cre >133 μmol/L. This study was approved by the ethics committee of Huashan Hospital following the principles of the Declaration of Helsinki. Written informed consent was obtained from all subjects.

We recruited 191 participants from the Leipzig Obesity Biobank. All participants fulfilled the following inclusion criteria: (1) age >18 years and (2) stable body weight, defined as the absence of fluctuations of >3% of body weight for ≥3 months before blood tests. In addition, the following exclusion criteria have been defined: (1) any acute or chronic inflammatory disease or symptoms of infection; (2) clinical evidence of either cardiovascular or peripheral artery disease; (3) smoking; (4) low-density lipoprotein cholesterol (LDL-C) >4 mmol/L; (5) any type of malignant disease; (6) thyroid dysfunction; (7) Cushing disease or hypercortisolism; (8) alcohol or drug abuse; or (9) pregnancy. The study was approved by the ethics committee of the University of Leipzig (approval number: 159-12-21052012) and all subjects gave written informed consent before taking part in the study.

Data Collections and Calculations

In the Chinese physical examination cohort, age, sex, weight, and height of all participants were recorded after registration. Fasting plasma glucose (FPG), total triglycerides (TG), total cholesterol, LDL-C, high-density lipoprotein cholesterol, ALT, aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and albumin serum concentrations were detected under fasting conditions in the morning. BMI was calculated as weight (kg) divided by height squared (m^2). BMI is categorized as underweight (BMI < 18.5 kg/m^2), normal (18.5 kg/m^2 ≤ BMI < 24 kg/m^2), overweight (24 kg/m^2 ≤ BMI < 28 kg/m^2), and obese (BMI ≥ 28 kg/m^2) (8).

In the Leipzig Obesity Biobank cohort, age, sex, weight, and height of all participants were collected. BMI is categorized as <40 kg/m^2 and ≥40 kg/m^2 (extreme obesity) in this cohort. REE was calculated based on measurements from indirect calorimetry with an open-circuit ventilated-hood system (Vmax Spectra 29n, SensorMedics BV, Viasys Healthcare, Bilthoven, The Netherlands). In our study, the RMR was calculated as REE (kcal/d)/body surface area (BSA) (m^2). BSA was calculated using the following equations: $BSA = 0.1173 \times \text{Weight (kg)}^{0.6466}$, which is validated for obese participants (9).

Measurement of Serum scEMC10 in Human

A total of 2 mL IV blood of all participants under fasting condition was collected and centrifuged to obtain serum. Serum specimens without hemolysis were stored in −80°C for further measurement of scEMC10 using chemiluminescent immunoassay kits (Phrenzer Biotechnology, Shanghai, China; RRID: AB_2934319), as described previously (5).

Statistical Analysis

Normally distributed data are presented as means ± SD, whereas skewedly distributed data are presented as median (interquartile range). TG, ALT, AST, GGT, REE, and RMR were logarithmically transformed and serum scEMC10 was fourth root–transformed before further analysis. Student *t*-test or ANOVA was used for continuous variables, and χ^2 test for categorical variables. Partial correlation analyses were performed to investigate the correlation between serum scEMC10 and REE after adjusting for BMI, and the correlations between RMR and BMI, age, and serum scEMC10 after adjusting for sex. Pearson's correlation analysis was used to examine the correlation between scEMC10 and other variables. Paraments that correlated significantly with serum scEMC10 were selected to enter stepwise linear regression by sex. We examined nonlinear association of serum scEMC10 with BMI by using restricted cubic spline curves with 3 knots and then visualized the curves with R. Three knots were at the 25th, 50th, and 75th percentiles of BMI. Because of the different distributions of age between the 2 sexes, we presented the scEMC10 concentration in different range of age separately by sex.

A 2-tailed *P* value <.05 was considered significant. All analyses were performed with Statistical Package for Social Sciences (version 26, SPSS, Chicago, IL, USA) and figures graphed with R (version 4.2.0) and GraphPad prism (version 8.0, GraphPad Software Inc.).

Results

Anthropometric Characteristics of Participants in a Chinese Physical Examination Cohort and a White Cohort

A total of 833 participants were enrolled in the Chinese physical examination cohort, including 55.7% males and 44.3% females whose ages ranged from 19 to 88 years (Table 1). These participants were divided into groups according to their BMI. The proportions of underweight (BMI < 18.5 kg/m^2), normal weight (BMI, 18.5-23.9 kg/m^2), overweight (BMI, 24-27.9 kg/m^2), and obese participants (BMI ≥ 28 kg/m^2) were 6.2%, 53.6%, 32.7%, and 7.5%, respectively. Significant differences in age, gender, BMI, FBG, ALT, GGT, and serum scEMC10 levels were observed among the 4 groups. However, there were no significant differences in TG, total cholesterol, high-density lipoprotein cholesterol, LDL-c, and AST (Table 1).

As shown in Table 2, we recruited 191 participants from the Leipzig Obesity Biobank whose REE was measured by using

Table 1. Anthropometric parameters and clinical characteristics of subjects in a Chinese physical examination cohort

	BMI (kg/m^2)				
Characteristics	<18.5 (N = 55)	18.5-23.9 (N = 473)	24–27.9 (N = 289)	≥28 (N = 66)	*P* value
Age, y	38.93 ± 16.45**	44.86 ± 13.89	46.1 ± 12.92	46.17 ± 12.20	.004[a]
Male/female	14/41*	204/269	221/68***	53/13***	<.001[b]
BMI, kg/m^2	17.4 ± 0.8***	21.4 ± 1.5	25.6 ± 1.1***	30.0 ± 2.0***	<.001[a]
FBG, mmol/L	5.17 ± 0.74	5.22 ± 0.69	5.46 ± 1.31**	5.34 ± 1.30	.008[a]
TG, mmol/L[c]	1.05 (0.75-1.53)	1.26 (0.83-1.83)	1.33 (0.88-1.87)	1.21 (0.95-1.90)	.155[a]
TC, mmol/L	4.93 ± 0.94	4.88 ± 0.91	4.89 ± 0.85	4.74 ± 0.85	.596[a]
LDL-C, mmol/L	3.10 ± 0.80	2.99 ± 0.81	3.06 ± 0.76	2.96 ± 0.82	.555[a]
HDL-C, mmol/L	1.34 ± 0.33	1.31 ± 0.33	1.26 ± 0.30	1.29 ± 0.33	.121[a]
ALT, U/L[c]	18.00 (13.00-27.00)	17.00 (12.00-27.00)	19.00 (13.75-31.25)*	21.50 (13.00-32.25)*	.010[a]
AST, U/L[c]	16.00 (19.00-25.00)	18.00 (16.00-22.00)	16.00 (19.00-24.00)	16.00 (18.00-25.00)	.108[a]
GGT, U/L[c]	16.00 (11.00-23.50)	17.00 (12.00-28.00)	19.00 (13.00-33.00)*	22.00 (13.75-44.00)**	.002[a]
scEMC10, ng/mL[d]	9.57 (3.91-15.34)	7.23 (3.29-13.81)	8.59 (3.88-17.42)*	10.71 (5.31-18.71)**	.014[a]

Abbreviations: ALB, albumin; ALT, alanine aminotransferase; AST, aminotransferase; BMI, body mass index; FBG, fasting blood glucose; GGT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; LSD, Fisher's least significant difference; scEMC10, secreted-isoform of endoplasmic reticulum membrane complex subunit 10; TC, cholesterol; TG, triglycerides.

[a]The *P* value for age, BMI, FBG, TG, TC, LDL-C, HDL-C, ALT, AST, GGT, ALB, and serum scEMC10 among 4 groups were obtained by 1-way ANOVA, and multiple testing was corrected by using LSD correction.

[b]The *P* value for gender among 4 groups was obtained by χ^2 test. The normal group was set to be the reference group.

[c]Log10 transformed before analysis.

[d]Fourth root transformed before analysis.

*$P < .05$, **$P < .01$, ***$P < .001$.

Table 2. Relationships of anthropometric parameters across serum scEMC10 quartiles in subjects from the Leipzig Obesity Biobank

Characteristics	Quartiles of scEMC10 concentration[a]				*P* value
	Quartile 1 (N = 48) (≤6.46 ng/mL)	Quartile 2 (N = 48) (6.46-16.50 ng/mL)	Quartile 3 (N = 48) (16.50-36.73 ng/mL)	Quartile 4 (N = 47) (≥36.73 ng/mL)	
Age, y	47.25 ± 9.19	43.90 ± 10.62	42.71 ± 10.95	43.45 ± 11.91	.070[b]
Male/female	15/33	13/35	12/36	9/38	.177[c]
BMI, kg/m^2	34.41 ± 7.45	35.26 ± 3.78	37.26 ± 6.08*	37.83 ± 6.74**	**.002**[b]
Height, m	1.71 ± 0.10	1.70 ± 0.09	1.69 ± 0.09	1.68 ± 0.09	.104[b]
Weight, kg	100.55 ± 24.65	102.00 ± 13.94	106.36 ± 21.09	106.83 ± 21.86	.084[b]
REE, kcal/d[d]	1881.5 (1684-2212.75)	1972 (1770-2174)	1929 (1766.75-2173.75)	1843 (1660-2099)	.678[b]
RMR, kcal/m^2/d[d]	846.63 (761.29-960.21)	848.49 (786.65-896.49)	829.64 (777.60-884.79)	805.10 (738.70-869.23)*	**.012**[b]

Abbreviations: BMI, body mass index; LSD, Fisher's least significant difference; REE, resting energy expenditure; RMR, resting metabolism rate; scEMC10, secreted isoform of endoplasmic reticulum membrane complex subunit 10.
[a]Fourth root transformed before analysis.
[b]The *P* values for age, BMI, height, weight, REE, and BMR among the 4 groups were obtained by 1-way ANOVA, and multiple testing was corrected by using LSD correction.
[c]The *P* value for sex among 4 groups was obtained by χ^2 test. The first quartile was set to be the reference group.
[d]Log10 transformed before analysis.
*$P < .05$, **$P < .01$.

indirect calorimetry, including 25.7% males and 74.3% females whose ages ranged from 19 to 60 years.

Serum scEMC10 Levels in Participants With Various BMI Levels

We determined serum scEMC10 levels of Chinese participants in 4 BMI strata. The median serum scEMC10 value in underweight, normal weight, overweight, and obese groups was 9.57, 7.23, 8.59, and 10.71 ng/mL, respectively. When compared with normal weight, both the overweight and obese groups have significantly higher levels of serum scEMC10 (Table 1, Fig. 1A). The nonlinear correlations between BMI and serum scEMC10 levels in participants from the Chinese physical examination cohort and the Leipzig Obesity Biobank cohort were modeled and visualized using restricted cubic splines. Strikingly, we observed a nonlinear correlation between serum scEMC10 and BMI in participants with BMI ranging from 16.0 to 36.0 kg/m^2 from the Chinese physical examination cohort (Fig. 1B, *P* nonlinear = .0226). However, the nonlinear correlation was not found in participants from the Leipzig Obesity Biobank cohort who had average BMI with 36.2 kg/m^2 (Fig. 1C, *P* nonlinear = .1012).

Serum scEMC10 Levels in Participants With Different Ages

In the Chinese physical examination cohort, the group of participants aged ≤30 years exhibited significantly higher serum scEMC10 levels than both groups aged 50 to 60 and older than 60 years. In addition, participants aged 30 to 40 years also had significantly higher serum scEMC10 levels than those aged 50 to 60 years (Fig. 2A). Serum scEMC10 levels in men aged 30 to 40 years were significantly higher than those in men aged older than 60 years. Women aged ≤30 years had significantly higher serum scEMC10 levels than both those aged 50 to 60 years and those older than aged 60 years (Fig. 2A). In participants from the Leipzig Obesity Biobank cohort, serum scEMC10 tended toward a decrease with age, which was more prominent in women (Fig. 2B).

Association Between RMR and Serum scEMC10 Levels

All 191 participants from the Leipzig Obesity Biobank were divided into quartiles according to their serum levels of scEMC10 (Table 2). Compared with participants in the first quartile, participants in the third quartile ($P < .05$) and the fourth quartile ($P < .001$) had significantly higher BMI, whereas participants in the fourth quartile had significantly lower RMR ($P < .05$). However, there was no significant difference in age, sex, height, and REE among the 4 groups (all $P > .05$). BMI was adjusted for applying a partial correlation analysis to examine the association of serum scEMC10 with REE. It showed a significantly negative correlation between serum scEMC10 and REE (partial $r = -0.251$, $P < .001$) (Fig. 3).

RMR was reduced in obesity (Fig. 4A). Participants with obesity at various levels (I obesity: 30 kg/m^2 ≤ BMI < 34.9 kg/m^2; II obesity: 35 kg/m^2 ≤ BMI < 39.9 kg/m^2; extreme obesity: BMI ≥ 40 kg/m^2) all had significantly lower RMR when compared with those without obesity (BMI < 29.9 kg/m^2) (all $P < .001$) (Fig. 4A). Men exhibited significantly higher RMR compared with women ($P < .001$)

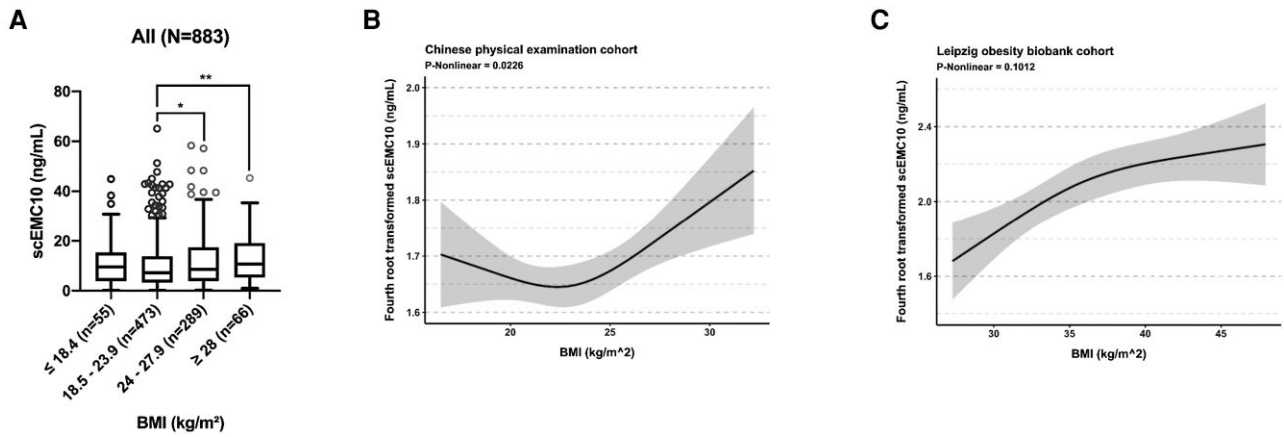

Figure 1. Serum scEMC10 levels in participants with different BMIs and their nonlinear association analyses in the Chinese physical examination cohort and the Leipzig Obesity Biobank Cohort. The *P* value for serum scEMC10 among BMI groups were obtained by 1-way ANOVA, and multiple testing was corrected by using LSD correction. Nonlinear association of serum scEMC10 with BMI was performed by using restricted cubic spline curves (RCS). scEMC10: Fourth root transformed before analysis. Abbreviations: BMI, body mass index; LSD, Fisher's least significant difference. **P* < .05, ***P* < .01.

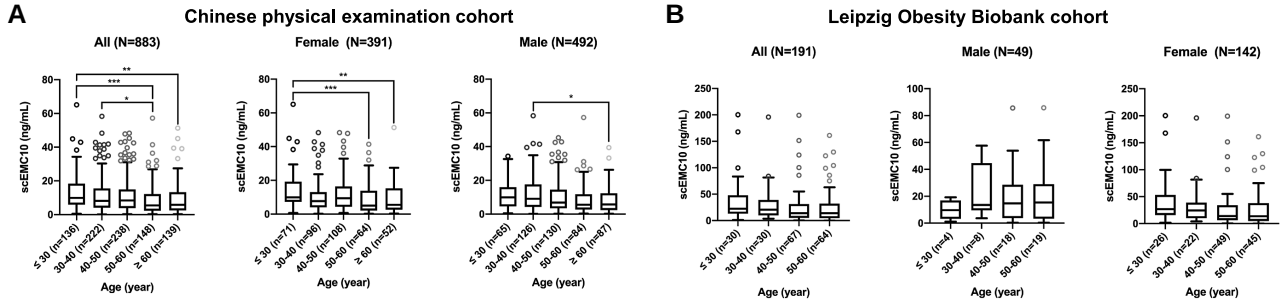

Figure 2. Serum scEMC10 levels in participants with age strata in the Chinese physical examination cohort and the Leipzig Obesity Biobank Cohort. The *P* value for serum scEMC10 among age strata was obtained by 1-way ANOVA, and multiple testing was corrected by using LSD correction. scEMC10: fourth root transformed before analysis. Abbreviation: LSD, Fisher's least significant difference. **P* < .05, ***P* < .01, ****P* < .001.

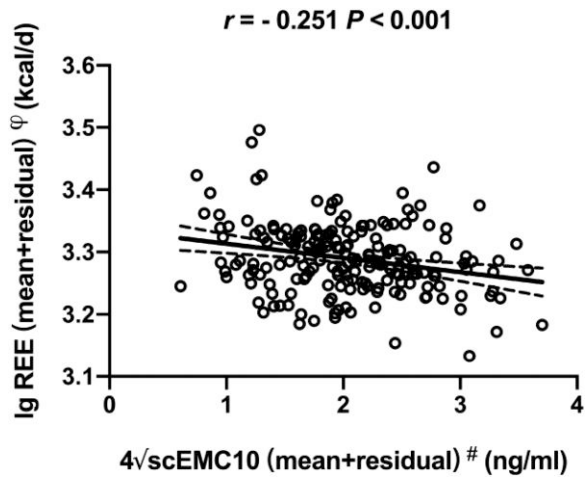

Figure 3. Partial correlation analysis of REE with serum scEMC10 after adjusting for BMI in participants from the Leipzig Obesity Biobank Cohort. ΦBMI-adjusted unnormalized residual via linear regression after addition of mean values of log10-transformed REE. #BMI-adjusted unnormalized residual via linear regression after addition of mean values of fourth root–transformed scEMC10. Partial *r* and *P* values were obtained after adjustment for BMI. Abbreviations: BMI, body mass index; REE, resting energy expenditure.

(Fig. 4B). In addition, participants aged 30 to 40 years had higher RMR than those aged 50 to 60 years ($P < .01$) (Fig. 4C). Following adjustment for sex, RMR was inversely associated with BMI (partial $r = -0.360$, $P < .001$), age (partial $r = -0.192$, $P = .008$), and serum scEMC10 (partial $r = -0.238$, $P < .001$) (Fig. 5A–C).

Correlation Analysis and Stepwise Linear Regression Analysis of Serum scEMC10 and Other Variables

Pearson's correlation analysis was used to investigate the relationship between serum scEMC10 levels and other variables displayed in Table 3. In the whole Chinese cohort, serum scEMC10 was negatively correlated with age ($P < .001$) and positively associated with BMI ($P < .05$). In men, serum scEMC10 was negatively correlated with age ($P < .001$) and positively associated with BMI, ALT, AST, and GGT (all $P < .05$). In women, serum scEMC10 was inversely associated with age, FPG, and GGT (all $P < .05$) (Table 3). In the Leipzig Obesity Biobank cohort, serum scEMC10 was significantly correlated with BMI ($r = 0.280$, $P < .001$) and RMR ($r = -0.236$, $P = .001$) in all participants. Similar correlations of serum scEMC10 with BMI ($r = 0.265$, $P = .001$) and RMR

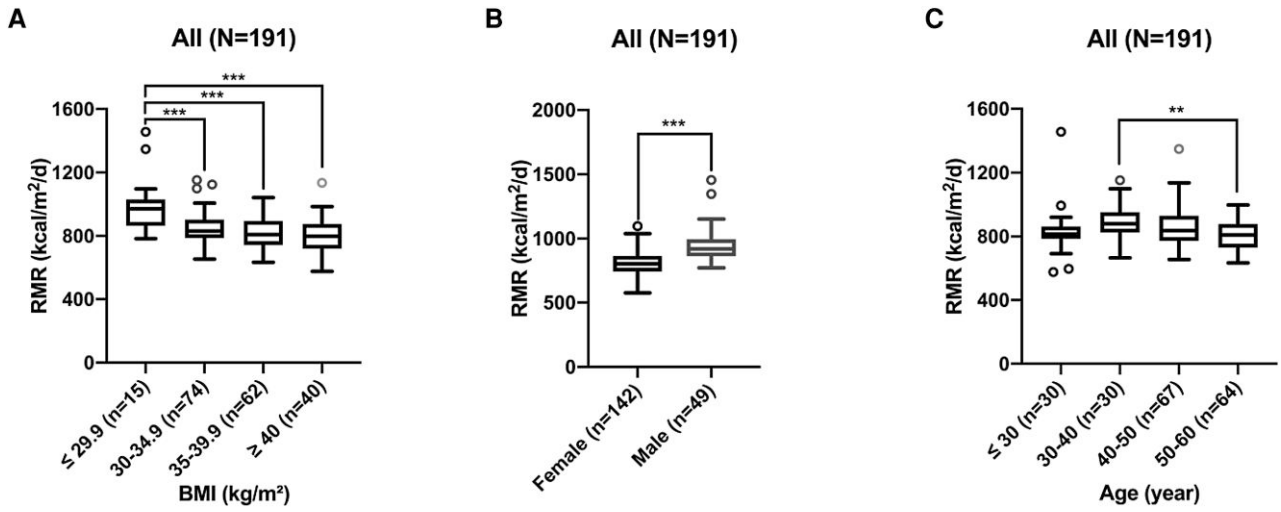

Figure 4. RMR levels in participants with different BMI, sex, and ages in the Leipzig Obesity Biobank Cohort. The *P* value for RMR among groups were obtained by 1-way ANOVA, and multiple testing was corrected by using LSD correction. The *P* value for RMR between males and females were obtained by Student *t*-test. RMR: Log10 transformed before analysis. Abbreviations: BMI, body mass index; LSD, Fisher's least significant difference; RMR, resting metabolism rate. $^{*}P < 0.05$, $^{**}P < .01$, $^{***}P < .001$.

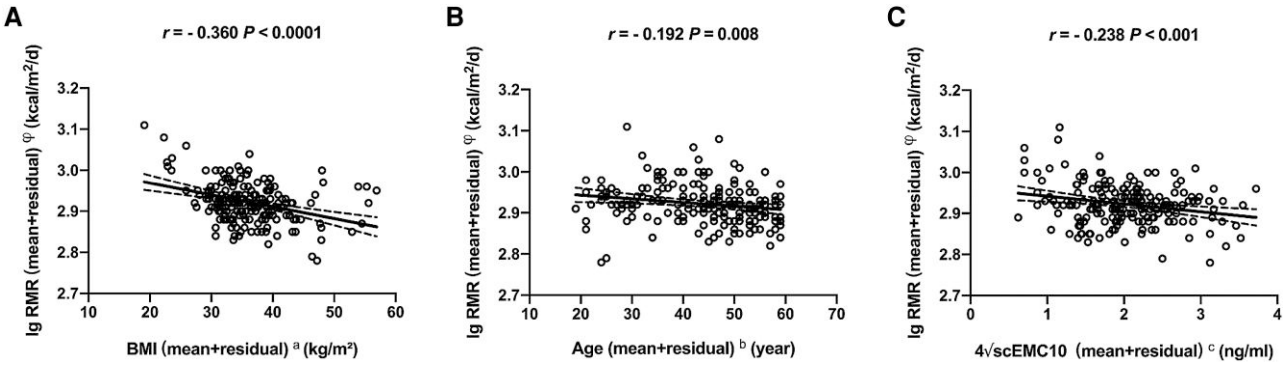

Figure 5. Partial correlation analyses of RMR with BMI, serum scEMC10, and age after adjusting for sex in participants from the Leipzig Obesity Biobank Cohort. [φ]Gender-adjusted unnormalized residual via linear regression after addition of mean values of log10-transformed RMR. [a]Sex-adjusted unnormalized residual via linear regression after addition of mean values of BMI. [b]Sex-adjusted unnormalized residual via linear regression after addition of mean values of age. [c]Sex-adjusted unnormalized residual via linear regression after addition of mean values of fourth root transformed scEMC10. Partial *r* and *P* values were obtained after adjustment for sex. Abbreviations: BMI, body mass index; RMR, resting metabolism rate.

($r = -0.235$, $P = .005$) were also observed in women. Moreover, serum scEMC10 inversely correlated with age in women ($P < .05$) (Table 3).

A multiple stepwise linear regression analysis was performed to characterize the relationship between serum scEMC10 and multiple clinical parameters. In the Chinese physical examination cohort, age, BMI, FPG, ALT, AST, and GGT were included for analysis. In all participants, serum scEMC10 was negatively associated with age ($P < .001$) and positively associated with BMI ($P < .05$), in an independent manner. In men, serum scEMC10 was also independently associated with AST (positive, $P < .05$) in addition to age and BMI. In women, only age was found to have an independent negative association with serum scEMC10 (Table 4). In the Leipzig Obesity Biobank cohort, age, BMI, REE, and RMR were included for analysis. Serum scEMC10 was positively associated with BMI ($P < .01$) and inversely associated RMR ($P < .05$), in the whole cohort, independent of other covariates. In women, serum scEMC10 inversely correlated with both age ($P < .05$) and RMR ($P < .001$), independent of other covariates (Table 4).

Discussion

Previously, we investigated the correlation between serum scEMC10 and obesity and observed that serum scEMC10 levels increase in overweight and obese subjects and positively correlate with BMI (5). In this study, the positive correlation was consistently observed in overweight or obese participants from 2 additional cohorts. Strikingly, we identified a J-shaped nonlinear correlation between BMI and serum scEMC10, which suggests that, besides overweight and obese people, underweight people also have higher serum scEMC10 than normal-weight people and implies that a low level of circulating scEMC10 is required for the homeostasis of body adiposity or weight. Our previous data support scEMC10 as an obesogenic circulating factor in mouse because scEMC10 overexpression promotes, whereas specific antibody

Table 3. Pearson's correlation analysis between serum scEMC10 levels and other variables in subjects from the Chinese physical examination cohort and the Leipzig Obesity Biobank

Variables	All		Male		Female	
	r	*P* value	*r*	*P* value	*r*	*P* value
Chinese						
Age	−0.143	**<.001**	−0.152	**<.001**	−0.124	**.014**
BMI	0.073	**.030**	0.111	**.014**	0.074	.147
FPG	−0.028	.411	0.018	.698	−0.106	**.037**
TG[a]	−0.055	.101	−0.017	.700	−0.096	.057
TC	0.015	.657	0.032	.482	−0.009	.863
LDL-C	0.047	.163	0.052	.246	0.039	.446
HDL-C	0.034	.317	0.017	.700	0.044	.385
ALT[a]	0.032	.344	0.110	**.015**	−0.046	.368
AST[a]	0.039	.246	0.105	**.021**	−0.057	.265
GGT[a]	0.000	.994	0.101	**.028**	−0.118	**.021**
German						
Age	0.142	.050	0.011	.940	−0.169	**.045**
BMI	0.280	**<.001**	0.270	.061	0.265	**.001**
RMR[a]	−0.236	**.001**	−0.162	.266	−0.235	**.005**

Abbreviations: ALB, albumin; ALT, alanine aminotransferase; AST, aminotransferase; BMI, body mass index; FBG, fasting blood glucose; GGT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; RMR, resting metabolism rate; scEMC10, secreted isoform of endoplasmic reticulum membrane complex subunit 10; TC, cholesterol; TG, triglycerides.
scEMC10, fourth root transformed before analysis.
[a]Log10 transformed before analysis.
$P < .05$ was bolded.

Table 4. A multiple stepwise linear regression analysis of the variables independently associated with serum scEMC10 levels in a Chinese physical examination cohort and the Leipzig Obesity Biobank cohort

Independent variables	Standardized *β*	t	95% CI	*P* value
Chinese				
All				
Age	−0.159	−4.659	−0.007 to −0.003	<.001
BMI	0.083	2.466	0.010 to 0.088	.014
Male				
Age	−0.171	−3.766	−0.008 to −0.002	<.001
BMI	0.098	2.161	0. 005 to 0.110	.031
AST[a]	0.096	2.118	0.020 to −0.529	.035
Female				
Age	−0.110	−2.157	−0.007 to 0.000	.032
German				
All				
BMI	0.202	2.700	0.006 to 0.035	.008
RMR[a]	−0.192	−2.565	−3.700 to −0.483	.011
Female				
Age	−0.183	−2.264	−0.019 to −0.001	.025
RMR[a]	−0.318	−3.928	−6.193 to 2.045	<.001

The analysis also included FPG, AST, and GGT, which were excluded in the final model.
Abbreviations: AST, aminotransferase; BMI, body mass index; FPG, fasting blood glucose; GGT, gamma-glutamyl transferase; RMR, resting metabolism rate; scEMC10, fourth root transformed before analysis.
[a]Log10 transformed before analysis.

neutralization prevents diet-induced obesity (5). It is unclear why a higher level of serum scEMC10 is present in underweight people than normal weight ones. Given the pro-obese property of scEMC10, the upregulation of scEMC10 is proposed as a compensatory mechanism, whereby underweight people maintain their body weight in response to further weight loss.

We used adjusted REE (RMR) by dividing by BSA to eliminate the metabolic effects of body size differences in the Leipzig Obesity Biobank cohort. RMR was inversely associated with BMI and age, and the RMR levels were significantly higher in men compared with women, which was consistent with other studies (10-13). It is noteworthy that RMR still exhibited a significant inverse association with BMI, age, and serum scEMC10 after adjusting for sex, respectively, suggesting these associations were independent of sex. We also observed a significantly negative association between serum scEMC10 and RMR in this cohort by performing multiple linear regressions. In a sex-stratified analysis, this inverse association between scEMC10 and RMR was observed in women, but not in men. However, it is hard to draw a conclusion that this association is sex dependent because men only account for a small portion (25%) in this cohort. RMR is a ratio measure (REE/BSA), which may have unfavorable statistical properties (14). The presence of BSA at the denominator may distort the relationship between serum scEMC10 and energy expenditure. Although there was no significant difference in REE among serum scEMC10 quartiles, the partial correlation analysis showed a significant inverse association between serum scEMC10 and REE after adjusting for BMI. This result agrees with mouse studies that demonstrate that overexpression of scEMC10 decreases, whereas neutralization of circulating scEMC10 increases energy expenditure accompanied by inhibiting PKA signaling and activating brown adipose tissue (BAT) thermogenesis (5). However, BAT activity has little impact on RMR in overweight or obese adults under thermoneutral circumstances (15). Fat-free mass, especially skeletal muscle tissues (accounts for 40%-50% of body weight), exhibits important effects on resting energy expenditure (16). We demonstrated that scEMC10 exerted an inhibitory effect on PKA signaling, which is involved in glucose and energy metabolism of skeletal muscle (5, 17). Therefore, the role of serum scEMC10 on energy metabolism of skeletal muscle warrants further investigation. However, fat-free mass was unavailable in this cohort, which was a limitation of this study.

Changes in circulating concentrations of hormones or cytokines occur with aging. Here, we observed that the serum levels of scEMC10 also vary with age. Generally, serum scEMC10 decreases with aging. In the Chinese physical examination cohort, serum scEMC10 significantly decreases in participants aged older than 50 years when compared with participants aged younger than 30 years, a decline that is more pronounced in women. Multiple regression analysis revealed that serum scEMC10 is negatively associated with age, independent of BMI and other covariates. The decrease of serum scEMC10 with aging is unlikely to be accounted for by the BAT mass or activity, which has been shown to be inversely associated with age in humans and to be enhanced by EMC10 ablation or antibody neutralization in mouse models

(5, 18, 19). As a limitation, we acknowledge that our data are based on cross-sectional cohorts. Therefore, longitudinal data are required to substantiate our findings. The changes of serum scEMC10 during aging are comparable to those of sex hormones in humans. In women, decreases of estrogens accompanied by increases of gonadotropins occur throughout menopause approximately 51 years old, with a range of variation between 40 and 60 years of age (20). Although men do not undergo an equivalent of menopause, concentrations of serum testosterone, dihydrotestosterone, and the testosterone precursor androstenedione are decreased gradually in their lifespans (21). In the future, the determination of the relationship between serum scEMC10 and sex hormones will provide clues regarding the physiological regulation of scEMC10; further investigations on the role of scEMC10 in aging are warranted.

In this study, we provided more evidence regarding the association of serum scEMC10 with BMI, observing a nonlinear J-shaped distribution of serum scEMC10 across BMI. We also identified an inverse association between serum scEMC10 and RMR, which is consistent with previous findings demonstrating that scEMC10 is a potential pro-obesity hormone. In addition, our work demonstrates a clear and consistent inverse association between chronological age and scEMC10, providing impetus to explore the significance of scEMC10 to human aging in future studies.

Acknowledgments

The authors thank Samuel M. Lockhart for his help in discussing the data and preparing the manuscript.

Funding

This work was supported by the National Natural Science Foundation of China (No. 81873645) and Science and Technology Commission of Shanghai Municipality (No. 22140902700) to X.C.W.

Disclosures

The authors have nothing to disclose.

Data Availability

All data generated or analyzed during this study are included in this published article or in the data repositories listed in References.

References

1. Liu L, Mao S, Chen K, *et al*. Membrane-bound EMC10 is required for sperm motility via maintaining the homeostasis of cytoplasm sodium in sperm. *Int J Mol Sci*. 2022;23(17):10069.
2. Wang XC, Xu SY, Wu XY, *et al*. Gene expression profiling in human insulinoma tissue: genes involved in the insulin secretion pathway and cloning of novel full-length cDNAs. *Endocr Relat Cancer*. 2004;11(2):295-303.
3. Junes-Gill KS, Gallaher TK, Gluzman-Poltorak Z, *et al*. hHSS1: a novel secreted factor and suppressor of glioma growth located at chromosome 19q13.33. *J Neurooncol*. 2011;102(2):197-211.
4. Wang X, Gong W, Liu Y, *et al*. Molecular cloning of a novel secreted peptide, INM02, and regulation of its expression by glucose. *J Endocrinol*. 2009;202(3):355-364.
5. Wang X, Li Y, Qiang G, *et al*. Secreted EMC10 is upregulated in human obesity and its neutralizing antibody prevents diet-induced obesity in mice. *Nat Commun*. 2022;13(1):7323.
6. Owen OE, Holup JL, D'Alessio DA, *et al*. A reappraisal of the caloric requirements of men. *Am J Clin Nutr*. 1987;46(6):875-885.
7. Sabounchi NS, Rahmandad H, Ammerman A. Best-fitting prediction equations for basal metabolic rate: informing obesity interventions in diverse populations. *Int J Obes (Lond)*. 2013;37(10):1364-1370.
8. Zhou BF. Effect of body mass index on all-cause mortality and incidence of cardiovascular diseases--report for meta-analysis of prospective studies open optimal cut-off points of body mass index in Chinese adults. *Biomed Environ Sci*. 2002;15(3):245-252.
9. Livingston EH, Lee S. Body surface area prediction in normal-weight and obese patients. *Am J Physiol Endocrinol Metab*. 2001;281(3):E586-E591.
10. Astrup A, Gøtzsche PC, van de Werken K, *et al*. Meta-analysis of resting metabolic rate in formerly obese subjects. *Am J Clin Nutr*. 1999;69(6):1117-1122.
11. French SA, Jeffery RW, Murray D. Is dieting good for you? Prevalence, duration and associated weight and behaviour changes for specific weight loss strategies over four years in US adults. *Int J Obes Relat Metab Disord*. 1999;23(3):320-327.
12. Da J, Long Y, Li Q, Yang X, Yuan J, Zha Y. Resting metabolic rate and its adjustments as predictors of risk protein-energy wasting in hemodialysis patients. *Biosci Rep*. 2021;41(4):BSR20210010.
13. Vlcek JS, Kocandrle VO. Renal function in patients with brain death with respect to early function after their transplantation. *Transplantation*. 1982;33(4):457.
14. Allison DB, Paultre F, Goran MI, Poehlman ET, Heymsfield SB. Statistical considerations regarding the use of ratios to adjust data. *Int J Obes Relat Metab Disord*. 1995;19(9):644-652.
15. van Marken Lichtenbelt WD, Vanhommerig JW, Smulders NM, *et al*. Cold-activated brown adipose tissue in healthy men. *N Engl J Med*. 2009;360(15):1500-1508.
16. Zurlo F, Larson K, Bogardus C, Ravussin E. Skeletal muscle metabolism is a major determinant of resting energy expenditure. *J Clin Invest*. 1990;86(5):1423-1427.
17. London E, Stratakis CA. The regulation of PKA signaling in obesity and in the maintenance of metabolic health. *Pharmacol Ther*. 2022;237:108113.
18. Cypess AM, Lehman S, Williams G, *et al*. Identification and importance of brown adipose tissue in adult humans. *N Engl J Med*. 2009;360(15):1509-1517.
19. Pfannenberg C, Werner MK, Ripkens S, *et al*. Impact of age on the relationships of brown adipose tissue with sex and adiposity in humans. *Diabetes*. 2010;59(7):1789-1793.
20. Broekmans FJ, Soules MR, Fauser BC. Ovarian aging: mechanisms and clinical consequences. *Endocr Rev*. 2009;30(5):465-493.
21. van den Beld AW, Kaufman JM, Zillikens MC, Lamberts SWJ, Egan JM, van der Lely AJ. The physiology of endocrine systems with ageing. *Lancet Diabetes Endocrinol*. 2018;6(8):647-658.